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Primary Sjögren's Syndrome and Autoantibodies

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Abstract

The presence of certain autoantibodies in the serum of patients facilitates the diagnosis of particular autoimmune diseases. Some antibodies may also be significant for the prognosis of the disease development and internal organs involvement. In the case of Sjögren's syndrome, it is known that overactivity of B-lymphocytes leads to the production of a number of autoantibodies—both markers for pSS (such as antibodies to ribonucleoproteins) and nonspecific antibodies (such as rheumatoid factor). The range of autoantibodies found in pSS is constantly expanding, but their significance is not fully established. At present, only anti-SS-A antibodies are introduced to the criteria for the pSS diagnosis. However, this does not stop an interest in other autoantibodies and the significance of their presence for the course of this disease. This chapter outlines the autoantibodies found in pSS and discusses their importance in clinical practice.

Keywords: primary Sjögren's syndrome, autoantibodies, clinical association

1. Introduction

Primary Sjögren's syndrome (pSS) is a chronic, persistent autoimmune disease with predominant B cells hyperreactivity and with the production of autoantibodies against intracellular antigens. Autoimmune process taking place in pSS affects exocrine glands primarily, causing their dysfunction and the development of symptoms of mouth and eye dryness. Through the formation of infiltrates consisting of different autoreactive cells (e.g., B and T cells, macrophages, and dendritic cells), pSS may affect other organs as well as whole systems (e.g., lungs, respiratory, urinary, and alimentary tract).

1.1. Triggering factors

In the pathogenesis of primary Sjögren's syndrome, certain genetic factors play a significant role, such as the presence of HLA-B8, HLA-DW3, HLA-DR3, and DRw52 genes or interferon regulatory factor 5 (IRF 5) gene polymorphism [1, 2]. Not only viral infections have been recognized as the pSS triggering factors, mainly Epstein-Barr virus (EBV) [3], but also human T-cell lymphotropic virus type-1 (HTLV-1), cytomegalovirus (CMV), and hepatitis C virus (HCV) [4, 5]. Bacterial infections *Staphylococcus aureus*, *Chlamydia pneumoniae*, *Chlamydia trachomatis*, *M. hominis*, *U. urealyticum*, and *H. pylori* may also play part in the development of pSS [6–8]. In many of the autoimmune rheumatic diseases, ultraviolet (UV) radiation is a recognized factor influencing the activity of the autoimmune process. The UV radiation causes movement of antigen molecules, bound with/to ribonucleoprotein, between cytoplasm and cell membrane (SS-A/Ro) and cell nucleus and cytoplasm (SS-B/La). UVB radiation affects epithelial damage, activates plasma dendritic cells, and increases the risk of their apoptosis and (risk?) of the IFN signaling pathway activation. Different observations concerning UVA radiation suggest that it inhibits the production of autoantibodies [9, 10].

The hormonal state of the individual may also play a role in the pSS development. The imbalance of sex hormones and its receptors, dependent on hypothalamic-pituitary-adrenal axis (HPA or HTPA axis), interferes with the ratio of estrogens to androgens, especially in genetically predisposed patients [11]. This influences the stimulation of the autoimmune process and may explain the more frequent occurrence of pSS in women, especially in middle-aged. In recent years, attention has been paid to the role of the deficiency of dehydroepiandrosterone (DHEA) and of DHEA-S, its metabolite, in pSS and other autoimmune diseases [12].

1.2. Outline of pathogenesis

As the epithelial cell damage and apoptosis provide basis for the pSS pathogenesis, the first step of the whole process is the activation of innate immunity, as the virus or bacteria antigen activates pattern recognition receptors (PRR) via Toll-like receptors (especially TLR 3, 7, 9). Activation of innate immunity leads, in turn, to the damage of epithelial cells, their apoptosis and the release of antigens and RNA complexes that strongly stimulate plasmacytoid dendritic cells (pDCs). These produce interferon alpha (IFN- α)—a factor strongly stimulating epithelial cells, dendritic cells and neutrophils to produce B-cell activating factor (BAFF) [13–16]. All processes initiating epithelial damage lead to the apoptosis of cells, activation of congenital and acquired immune systems and the cascade effect of pathophysiological phenomena, resulting primarily in the overproduction of BAFF and other B-cell stimulating cytokines including APRIL (proliferation inducing ligand), similar in its actions to BAFF. Both BAFF and APRIL belong to the tumor necrosis factor superfamily (TNF) [17, 18]. The antigens released from damaged cells, primarily SS-A and SS-B ribonucleoproteins are targets for B cells and cause the production of specific anti-SS-A/Ro and anti-SS-B/La autoantibodies. Plasmacytoid dendritic cells also stimulate T lymphocytes, particularly the CD4+ subtype, which is later the main component of infiltrates in the endocrine glands. The Th1-type immune response is predominant, with activation of Th17 cells secreting interleukin 17 (IL-17). Th1 cells produce IFN- γ , which, in addition to the increase of BAFF secretion, induces the production of plasminogen

activator, which—simultaneously with IL-17—causes the development of local inflammatory process. As a result of the abovementioned changes, leading to the hyperstimulation of B lymphocytes, autotolerance is disturbed and further production of autoantibodies [19].

2. Autoantibodies in primary Sjögren's syndrome

2.1. Antinuclear antibodies

A primary test for autoantibodies, finding the use in the diagnostics of pSS and other systemic autoimmune rheumatic diseases (SARD), is the determination of anti-nuclear antibodies (ANAs) [20, 21]. ANA are found in 80–90% of patients with pSS. These antibodies react with the components of the cell nucleus and are most often tested with indirect immunofluorescence (IF) on HEp-2 (human epithelial cell) cell line. In pSS, ANA often occur in higher titers (above 1:320), but may be also detected in lower titers (1:160) and in the concurrent presence of other autoantibodies. In **Table 1**, the prevalence of ANA antibodies in different autoimmune diseases was presented.

In recent years attention has been paid to the frequent occurrence of dense fine speckled pattern (DFS70) on HEp-2 in both healthy people and patients with ANA associated autoimmune rheumatic diseases (AARD). DFS70 antibodies bind a ubiquitinated protein called lens epithelium derived growth factor (LEDGF), which occurrence was associated in first observations [22] with asthma and atopic dermatitis. However, the high prevalence of DFS70 autoantibodies in normal population, without any symptoms of any AARD, was observed. Therefore, in the case of positive result of the screening for ANA antibodies in individuals without symptoms suggestive of a systemic autoimmune rheumatic disease (SARD/AARD), it is advisable to detect DFS70 antibodies using specific tests (e.g., ELISA/EIA; CLIA/CIA) [23, 24]. Even up to 1/3 of positive cases for ANA are also positive for DFS70 antibodies [23, 24].

2.2. Extractable nuclear antigens

In 1959, Holman et al. recorded a reaction of sera from SLE patients with extractable nuclear antigens (ENA) isolated from a crushed calf thymus. This observation confirmed the reaction of autoantibodies in the SLE sera with soluble nuclear antigens. The nomenclature of ENA autoantibodies derived from the group, in which they were first described, and corresponds to the nuclear function of the antigen (RNP) or the name of the patient providing the prototype serum (Ro, La, Sm, Jo, Mi), as well as the disease from which the patient suffered (SSA,

Disease	SLE	SSc	pSS	MCTD
ANA sensitivity%	95	70–90	50–80	90

SLE—systemic lupus erythematosus; SS, SSc—systemic sclerosis, pSS—primary Sjögren's syndrome, MCTD—mixed connective tissue disease.

Table 1. Prevalence of ANA antibodies in different autoimmune diseases [20, 21].

SSB, SSC, Scl-70, PM-1, PM-Scl) [23]. The set of all ENA includes more than 100 soluble and cytoplasmic antigens. In clinical practice, until present day, only few of the them are finding use as a immunological hallmarks of certain autoimmune diseases or being used as immunological prognostic factors. Among them the most prominent are as follows: anti-RNP (anti-ribonucleoprotein anti-U(1)RNP), anti-Sm RNP, anti-SSA/Ro, anti-SSB/La, anti-Sm (Smith) antibody, anti-Scl-70 (anti-topoisomerase antibodies), anti-Jo-1 (anti-histidyl-transfer RNA synthase antibodies). The pattern of positive and negative results obtained with an ENA panel should be evaluated in conjunction with all clinical findings. Main autoantibodies and disease which they are typical to are presented in **Table 2**. Selected autoimmune diseases along with their predominant autoantibodies are presented in **Table 2**. **Figure 1** shows a simplified diagnostic algorithm of immunological diagnosis.

2.3. Characteristics of ENA antibodies and their connection with primary Sjögren’s syndrome

From 1981, it is known [26] that SS-A/Ro antigens are associated with small cytoplasmic RNAs. In 1984 Ro60 kD protein was discovered and Ben-Chetrit et al. in 1988 demonstrated second part of SS-A/Ro complex—a 52 kD protein [25–27]. As we have recently learned, the SS-A/Ro antigen consists of two different proteins Ro60 and Ro 52, with different gene localization: Ro60 is located on chromosome 19, while Ro-52 on chromosome 11. It was also revealed that these antigens, in physiological conditions, are found in different cell compartments. The detection of their presence determines different clinical implications. Presently, this problem needs still further investigation.

SS-A/Ro (60KD + 52KD) is a complex present on most cells, including platelets and red blood cells. It is considered that the anti-SS-A antibody plays a pathogenic role in pSS and its presence is associated with more severe symptoms, resulting from the involvement of endocrine glands, lymphadenopathy, larger salivary glandular infiltrates, characteristic vasculitis and longer duration of the disease [28, 29]. Also the occurrence of interstitial lung disease (ILD) is

Disease.	RA	pSS	MCTD	SLE	dSSc	lSSc	PM	DM	GPA	MPA
Antibodies	ACPA RF	Anti-SS-A/Ro60 Anti-SS-A/Ro52 Anti-SS-B/LA RF	RNP RF	Anti-dsDNA Anti-Sm Anti-Ro60	Anti-Scl-70	Anti-CENP-A,B,C	Anti-Jo-1 Ro-52 Other anti-synthetase antibodies, Anti-Mi-2 Anti-SRP	Anti-Ro-52 Anti-Mi-2	cANCA	pANCA

RA—rheumatoid arthritis; pSS—primary Sjogren’s syndrome; MCTD—mixed connective tissue disese; SLE—systemic lupus erythematosus; dSSc—disseminated systemic sclerosis, lSSc-localized systemic sclerosis; PM—polymyositis; DM—dermatomyosistis; GPA—granulomatosis with polyangiitis; MPA—microscopic polyangiitis.

Table 2. Autoimmune diseases and main autoantibodies [20–24].

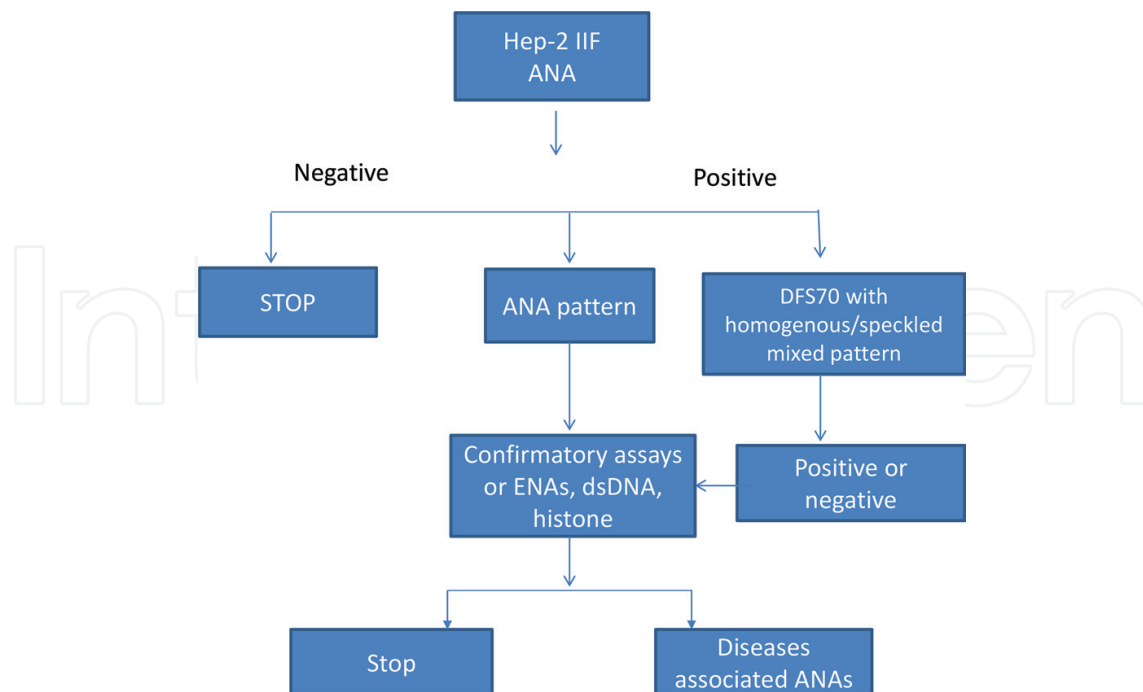


Figure 1. Simplified algorithm of immunological diagnosis of rheumatic diseases [22–24]. ANA—antinuclear antibodies; DFS70—dense fine speckled pattern antibodies; ENAs—extractable nuclear antigens; dsDNA—anti-double stranded DNA antibodies.

associated with the presence of antibodies against SS-A/Ro antigens, primarily Ro52KD and is associated with a higher degree of inflammatory changes in the salivary glands.

The formation of anti-SS-A is affected by the UV radiation, which increases the expression of antigens on the cell surface. Anti-SS-A/Ro antibodies are considered as a triggering factor for photosensitivity in SCLE and NLE, although patients with DLE, but without anti-Ro antibodies, present skin changes after sun/light exposition as well, probably due to other pathomechanism (the presence of autoantibodies/immunoglobulins between skin and the epidermis) [30].

Ro60 antigen attaches to uncoded RNA to form a complex (hY-RNA) that plays a role in inhibiting the immune response. Ro52 antigen is a phosphoprotein forming due to stimulation by viral infection, type I interferon pathway and through Toll-like receptors [28].

2.3.1. Anti-SSA/Ro antibodies

Autoantibody Ro60 has been associated with Sjögren's syndrome in particular but also occur in SLE (50%), and subacute cutaneous lupus (SCLE) (60%) and neonatal lupus (NLE) [31]. Anti-Ro antibodies in SLE and SCLE are associated with photosensitivity and skin changes (SCLE, NLE). In SCLE, negative results for ANA screening or finding ANA in low titer do not exclude the presence of anti-SSA/Ro antibodies (antibody—negative SCLE). Anti-SS-A antibodies are also found in systemic sclerosis, RA and polymyositis, as well as dermatomyositis (PM/DM) and autoimmune hepatitis, with antibodies to the Ro52 antigen present more frequently. Anti-Ro52 antibodies frequently occur in association with anti-Ro60 antibodies,

especially in the context of SLE, Sjögren's syndrome, subacute cutaneous lupus and neonatal lupus congenital heart block [31, 32]. However, the presence of anti-Ro52 alone, without anti-Ro60, was reported in inflammatory myopathy and in systemic sclerosis. It was also observed, that anti-Ro52 antibodies are, to larger extent than anti-Ro60, associated with primary biliary cirrhosis (PBC) and autoimmune hepatitis (AIH) with co-expression of anti SLA antibodies (soluble liver antibodies) [33].

2.3.2. Anti-SS-B/La antibodies

Anti-SS-B/La antibodies are less common and usually coexist with anti-SS-A antibodies, and their presence in other systemic diseases, especially in SLE (25% of patients with TRU), is associated with skin lesions (erythema, alopecia), inflammation of the serous membranes, leukopenia, symptoms of dryness and they often coexist with the presence of anti-SS-A antibodies (secondary SS) [28]. Rao et al. have noted that anti-SSB antibodies are important for the SLE diagnosis. They are associated with cheek erythema, alopecia, serositis, secondary Sjögren's syndrome, and hematological changes such as leukocytopenia, thrombocytopenia, and immunoglobulins elevation. They are often accompanied by the presence of anti-/Ro or anti-SSA/Ro52 antibodies [34]. These autoantibodies may also be found before the SLE-specific antibodies can be detected [35].

3. Rheumatoid factor

Rheumatoid factor (RF) is an autoantibody directed against the CH2 and CH3 domains of an Fc region of a class G immunoglobulin (IgG). RF is produced by plasmatic cells (RF-PCs) that are formed from B cells activated both dependently and independently of T lymphocytes. Thus, RF producing B cells (RF-PC) become cells with ability of antigen presentation (APC) and of binding IgG. As this cascade of events constitutes a method of immune response against the infectious antigens, the RF production during infections protects the host organism. This phenomenon explains the occurrence of RF in the course of many viral (e.g., HCV, Herpes virus, and HIV), bacterial (e.g., subacute bacterial endocarditis, *Chlamydia pneumoniae*, *Klebsiella pneumoniae*, tuberculosis, and syphilis) and even parasitic (malaria, onchocerciasis, and toxoplasmosis) infections. In those autoimmune diseases, in which B-cell hyperactivity occurs, rheumatoid factors, particularly clinically relevant RF-IgM, also appears [36]. It should be remembered that RF appears in 4% of a healthy population and its incidence increases with age; after 75 years of life, RF can be observed even in 10–25% of individuals [37, 38]. The frequency (%) of RF in various CTD is presented in **Table 3**. The primary Sjögren's syndrome is one of the autoimmune diseases in which the majority of patients have a rheumatoid factor (some authors report up from 60 to 90% of patients)—specifically its most common IgM class isotype. The presence of RF IgM is associated with the occurrence of leukopenia, increased erythrocyte sedimentation rate (ESR), higher concentration of gamma globulins and lower C4 complement component concentration. Observations of a positive correlation of the rheumatoid factor with symptoms of dryness, hypergammaglobulinemia, presence of higher ANA antibody titers, presence of

Autoimmune connective tissue disease	RF frequency%
Primary Sjögren's syndrome	75–90
Rheumatoid arthritis	70–90
Mixed connective tissue disease	50–60
Systemic sclerosis	20–30
Systemic lupus erythematosus	15–20
Dermato/polymyositis	20
Vasculitis (GPA and MPA)	5–20
Other CTD* as psoriatic arthritis, juvenile idiopathic arthritis, and reactive arthritis	5 and <5

Table 3. The frequency of RF in various connective tissue diseases [39].

anti-SS-A antibodies, anti-SS-B, increased ESR and leukopenia were presented in their work by Witte et al. [39]. The presence of RF in patients with pSS, as well as in other autoimmune diseases, and in acute infections, indicates the formation of a large number of other antibodies and the formation of antigen complexes with antibodies. The frequency of RF in various CTD was presented in **Table 3** [39].

4. Other autoantibodies

4.1. Anti-centromere autoantibodies

Anti-centromere antibodies (ACA) are directed to six antigens associated with centromere (composed of a complex of kinetochore proteins). Currently identified anti-centromere antibodies (CENP) have been assigned designations with letters from A to F. The most common are CENP-A, B and C. CENP-B is also the most frequently occurring anti-centromere antibody in patients with pSS. The incidence of ACA antibody described in the literature ranges from 3.7 to 4% [40, 41]. This antibody, with a mass of 80 kDa, is a DNA-binding protein involved in the heterochromatin folding. Anti-centromere antibodies (A, B, C) occur mainly in limited systemic sclerosis (LSSc) and are associated with the prevalence of telangiectasia, higher severity of Raynaud's symptom, lung involvement such as interstitial lung disease [ILD] and fibrosis [42]. Their relationship between the presence of ACA antibodies and the involvement of endocrine glands has been demonstrated; in the ACA+ group, anti-SS-A and anti-SS-B autoantibodies were less frequent [42].

The association of ACA antibodies with non-Hodgkin's lymphomas (CENP-F) including MALT lymphomas was also described [43], as well as the case reports of CENP-B presence in small-cell lung cancer [44].

Interestingly, it has also been demonstrated that the presence of anti-CENP-B antibodies is associated with prolonged survival in a breast cancer [45].

4.2. Antibodies against citrullinated proteins

Citrullination is the post-translational process in proteins of deamination/conversion of the amino acids: arginine into citrulline. ACPA positive sera include antibodies to citrullinated proteins, such as fibrin and fibrinogen, vimentine (MCV—mutated citrullinated vimentine) and alpha-enolase (CEP-1).

It is known that arthritis may be one of the clinical symptoms of pSS. However, most of the pSS patients suffer from arthralgia, and only minority develop non-destructive arthritis. ACPA antibodies, a main marker of rheumatoid arthritis, are usually present in low concentrations in pSS according to various studies they are present in 3–22% of cases [46]. A higher incidence of arthritis was found in pSS patients with ACPA presence compared to patients without these antibodies [47]. It seems, however, that patients with pSS and ACPA positive require further observation toward the development of rheumatoid arthritis [48].

It should also be remembered that smoking and periodontal infection by *Porphyromonas gingivalis* are strong environmental factors stimulating protein citrullination and the emergence of ACPA antibodies [49].

4.3. Citrullinated alpha-enolase

Citrullinated alpha enolase (CEP-1) is an antigenic target for antibodies against citrullinated proteins (ACPA). In the Nezos et al. study [50], it was shown that CEP-1 antigen is a major antigen target in the ACPA positive subgroup of patients with pSS. The frequency of CEP-1 antibody in the RA ACPA positive group was not as high, while it was not found healthy group at all. The authors drew attention to the link of anti-CEP-1 antibodies presence to arthritis as well as to renal tubular dysfunction.

4.4. Antibodies recognizing salivary gland and lacrimal gland tissue

In recent years, researchers identified autoantibodies to carbonic anhydrase 6 (anti-CA6 antibodies), anti salivary gland protein 1 (SP-1) and anti-parotid secretory protein (PSP) [51]. These antibodies may emerge before pSS marker antibodies such as SS-A/Ro or SS-B/La and are associated with a minor focus score; these antibodies also occur more often in patients who did not have anti-SS-A/Ro antibodies [52]. Interestingly, in Langhe et al. work, anti CA6-IgA antibodies were detected primarily in patients with long pSS duration; other autoantibodies such as anti-CA6, PSP, and SP1 in IgG and IgM class were more frequently observed in SSc and MCTD with secondary SS. These autoantibodies do not allow distinguishing SLE from secondary SS. However, the described study was limited by a small group of SLE patients [52]. In the literature, some cases have been reported of patients with severe symptoms of eye or mouth dryness, in which there was no SS-A/Ro antibodies, but the presence of anti SP-1 antibody was confirmed [53]. It may suggest, that in case of a patients presenting unexplained dryness with no serology markers defined in current criteria for pSS, performing the test for novel, early antibodies to Sp1 and PSP may still be useful for diagnosing patient's condition [53].

4.5. Anti-muscarinic antibodies

Muscarinic 3 receptor (M3R) is found in various places in the body, such as smooth muscles, the endocrine and the exocrine glands, lungs, pancreas and even the brain. This receptor is also expressed on pancreatic beta cells, modulating insulin secretion. Activation of the M3R receptor induces smooth muscle constriction and increase glandular secretions [54].

It has been demonstrated that muscarinic acetylcholine type 3 receptor (M3R) antibodies are present in the serum of patients with pSS [54]. As it was presented by Kovacs et al., M3R antibodies are found in up to 90% of subjects with pSS [55]. In the group with M3R antibodies, leucopenia was more frequently observed [55]. Immune response to muscarinic receptor 3 plays a role in the pathogenesis of autoimmune sialoadenitis [56] and diabetes mellitus type 2. M3R antibodies may be present in other autoimmune diseases and do not allow for differentiation between primary and secondary Sjögren's syndrome. The severity of symptoms of dryness or dysfunction of the exocrine system in pSS may be related not only to M3R antibodies presence but also to other autoantibodies such as, for example, antibodies to aquaporins [57].

4.6. Autoantibodies to aquaporins

Aquaporins (AQP; water channels) are integral membrane proteins that form pores in the membrane of biological cells, enabling transport of water between cells. Some genetic defects of aquaporin genes have been associated with diseases as neuromyelitis optica (Devic's syndrome) and nephrogenic diabetes insipidus. First, aquaporin—"aquaporin-1" was described in 1992 by Peter Agre, until today we know 13 aquaporins, of which four are best defined [58]. Because of their influence of water transport, aquaporins have an impact on saliva and tear production and changes in AQP expression may lead to dryness symptoms [59, 60]. Aquaporin-4 (AQP4) is found on perivascular and ependymal cells, but it has also been discovered in sera of patients with NMO and multiple sclerosis. Tzartos and his colleagues detected aquaporin antibodies (AQP-1, -3, -8, and -9) in pSS patients sera [61]. What is interesting in the pSS group, AQP-4 and AQP-5 antibodies were not present. The presence of AQP antibodies was associated with more severe xerophthalmia; the authors suggest potential role of AQP-Ab in salivary gland secretions. Such hypothesis requires further research.

4.7. Autoantibodies binding to stathmin-4

Stathmins (STMN) are phosphoproteins which play a role in neuronal development and interact with tubulin. Presently, four stathmins have been identified. Stathmins are upregulated in a number of cancers and neuropathies [62]. Anti-stathmin-4 antibodies in IgG3 class were proposed as a biomarker of polyneuropathy and such observations were presented by Duda et al. in their study. The authors described anti-STMN4 antibodies in 33% of pSS patients with polyneuropathy (PNP)—vs. 7% of those without PNP—and in 45% of individuals with vasculitis skin changes (as opposed to 13% in individuals without them) [63].

4.8. Anti-alpha-fodrin antibodies

Alpha fodrin is an actin-binding, organ-specific protein of the cytoskeleton. Antibodies against alpha-fodrin are detected in serum samples from patients with primary or secondary Sjögren’s syndrome especially with sicca symptoms. Some authors suggest that they can be detected earlier in the course of pSS, sometimes before the emergence of anti SS-A or SS-B antibodies [64]. These antibodies, in the IgA and IgG class of immunoglobulins, are found in the serum and salivary glands of patients with pSS. However, other researchers did not describe any significant sensitivity and specificity of these antibodies [65–67].

4.9. Autoantibodies in saliva that may be relevant in pSS associated with the development of MALT lymphoma

Major salivary glands are the main extra endocrine glands targeted in pSS and saliva of patients with pSS is also a source of antibodies and cytokines. Large salivary glands are also the site for MALT lymphoma development. Investigators are interested in finding biomarkers in saliva, that allow for early pSS diagnosis, as well as the detection of mucosa associated lymphoma (MALT lymphoma). Cui et al. suggest set of three autoantibodies such as anti-cofilin-1 antibodies, anti-alpha enolase and anti-Rho GDP dissociation inhibitor 2(RGI2) antibodies, which, due to high specificity and sensitivity, may play a role as such biomarkers [68].

5. Autoantibodies in course of pSS—summary

In the current pSS criteria, only anti-SS-A/Ro antibodies are taken into account as the most sensitive and specific for pSS diagnosis. Still, the multisymptom picture of this rheumatic disease compels the search for other immunologic markers of at least equal prognostic importance.

Auto-antibody	Clinical findings
Anti-Ro52 kD	Interstitial lung disease
Anti-Ro60 kD	Hematologic changes, photosensitivity, skin involvement, Raynaud’s phenomena, and dryness
Anti-SS-B/La	Liver (autoimmune disease) PBC
RF	Dryness, hypergammaglobulinemia, and leukopenia
ACPA	Arthralgia and arthritis
Anti-CENP-B	Interstitial lung disease and fibrosis
Novel autoantibodies	
Anti-CA6	Dryness and renal tubular acidosis
Anti-PSP	Dryness
Anti-SP1	Dryness
Anti-CEP-1	Arthritis and renal tubular dysfunction.

Table 4. Antibodies in pSS and their association with clinical manifestation.

The occurrence of some of the identified antibodies has been associated with the specific clinical features such as interstitial lung disease, increased eye dryness, increased risk of nephrolithiasis and tubular distal acidosis or MALT lymphomas. In **Table 4**, autoantibodies frequently occurring in pSS and their association with clinical manifestation were presented.

6. Conclusions

pSS is a still not fully understood autoimmune disease, requiring doctor's vigilance. Even despite of a pSS having a mild course for a long time, there is a risk of organs and systems involvement. As it has been known for many years already, the risk of developing lymphomas is particularly increased in pSS patients compared to the healthy population. Although only one antibody (SS-A/Ro) has been included in the pSS diagnostic criteria, a lot of attention has been paid to new autoantibodies that can help clinicians in patient stratification in the early stages of diagnosis or may have a prognostic value.

Conflict of interest

The authors declare no conflict of interest.

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